

New Knowledge About HGH

THE PAST DECADE has witnessed an explosion of new knowledge concerning the structure, secretion and function of human growth hormone (HGH). During this short time, HGH was purified and shown to be effective in the treatment of hypopituitary dwarfism; a specific HGH immunoassay was developed, leading to a rapid increase in our knowledge concerning the regulation of growth hormone secretion and providing a specific test for the diagnosis of growth hormone deficiency and hypersecretion; the primary amino acid sequence of the HGH molecule was determined, and within the past year this complex peptide hormone was synthesized.

Elsewhere in this issue, VanderLaan has reviewed the control of growth hormone secretion in man. It is apparent that the regulation of growth hormone secretion and the mechanisms of HGH action are quite complex. As with the other pituitary hormones, the secretion of HGH appears to be regulated by a specific hypothalamic releasing factor or hormone (GRF or GRH).¹ Although the purification of GRF and determination of its structure have not yet been accomplished, it is likely that GRF will prove to be a short peptide molecule, similar to thyrotropin releasing factor (TRF) and melanocyte stimulating hormone inhibiting factor (MIF).² The numerous stimuli for HGH secretion, both chemical and neuronal, appear to act on the hypothalamus, releasing GRF into the hypothalamic-hypophyseal portal veins, which then stimulates HGH release from the pituitary gland. The physiological regulation of HGH secretion, however, has still not been completely unraveled. VanderLaan has reviewed the various pharmacological and stressful stimuli of HGH secretion, as

well as the recent experiments which have demonstrated a spontaneous peak in plasma HGH concentrations following the onset of sleep. Recent evidence also suggests that growth hormone can regulate its own secretion by means of an auto-feedback system. The plasma HGH response to both insulin-induced hypoglycemia and arginine infusion are markedly attenuated following increases in the plasma concentration of HGH (for example, following exercise) or following exogenous HGH administration.^{3,4} Complete understanding of the normal daily regulation of HGH secretion however, will require the development of techniques which can monitor HGH secretion rates over long periods of normal activity; a promising method has recently been described by Kowarski et al.⁵

The mechanisms of action of HGH on the peripheral tissues are also quite complex. Aside from its obvious role in the stimulation of growth and protein synthesis, HGH appears to play an important part in the daily regulation of fat and carbohydrate metabolism.⁶ HGH is an important stimulus of lipolysis, elevating plasma free fatty acid concentrations; it directly augments the pancreatic secretion of insulin and antagonizes the peripheral effects of insulin on glucose uptake. Most of these metabolic effects appear to be secondary to the direct action of HGH on RNA and protein synthesis. The effects of HGH on cartilage metabolism and bone growth, however, appear to be indirect, involving the participation of a secondary hormonal mediator.⁷ Salmon and Daughaday⁸ demonstrated that serum from normal individuals contains a hormonal substance which stimulates sulfate uptake in cartilage; they named this material "sulfation factor" (SF). Sulfation factor is deficient in the serum of hypopituitary persons, but can be induced within 24 to 48 hours by treating them with HGH. Addition of HGH to hypopituitary serum *in vitro*, however, does not induce sulfation factor activity. Furthermore, hypophysectomized rat cartilage removes sulfation factor activity from serum *in vitro*, but has little HGH-

binding activity.⁷ Thus HGH appears to induce the generation of sulfation factor (probably in the liver), which in turn stimulates cartilage anabolism and replication. Daughaday⁷ has suggested that the intermittent and irregular pattern of HGH secretion would be a poor system for the regulation of orderly cell growth; the sulfation factor system may have evolved to integrate the net effect of multiple HGH peaks, thus providing a modulated system for the regulation of bone growth.

Disorders of HGH secretion have long been recognized: acromegaly and gigantism resulting from excessive HGH secretion, and proportionate dwarfism from HGH deficiency. VanderLaan has reviewed the complexity of the hypothalamic and pituitary abnormalities in the etiology of acromegaly. It is now apparent that pituitary dwarfism is a heterogeneous group of disorders which result from disturbances in all parts of the hypothalamic-hypophyseal-target organ complex.⁹ A clinical syndrome of pituitary insufficiency might theoretically result from developmental or degenerative diseases of the hypothalamus, deficiency of hypothalamic releasing hormones, developmental or degenerative lesions of the pituitary, deficient secretion or structural abnormalities of the pituitary hormone molecule, or by target organ unresponsiveness to hormonal action. Examples of most of these mechanisms have been documented in the pathogenesis of pituitary dwarfism.⁹ Hypothalamic abnormalities associated with HGH deficiency have been described in association with the holoprosencephaly syndromes,¹⁰ anencephaly¹¹ and septo-optic dysplasia.¹² HGH deficiency secondary to degenerative hypothalamic destruction has been described in histiocytosis X.¹³ Congenital absence of the pituitary¹⁴ and degenerative lesions of the pituitary (for example, hemochromatosis¹⁵) have been found to result in HGH deficiency. Target organ unresponsiveness to the actions of HGH appears to be the cause of the African pygmies' short stature;¹⁶ whereas in Laron type of dwarfs the basic defect appears to involve either an inability to generate sulfation factor, or a structural mutation in the HGH molecule.¹⁷

Among the idiopathic forms of pituitary dwarfism, several mechanisms are likely, including a deficiency or structural defect in either CRF or the HGH molecule itself. Costom, Grumbach and Kaplan¹⁸ recently demonstrated that the primary defect in many panhypopituitary dwarfs lies in the

hypothalamus rather than the pituitary. They found that eight of nine hypopituitary dwarfs tested had a normal TSH response to exogenously administered TRF, indicating that the primary cause of their hypothyroidism was a deficiency of TRF. It is thus likely that their HGH deficiency is also due to deficient CRF secretion. The major implication of this important observation is that CRF may provide a practical substitute for HGH in the treatment of many patients with pituitary dwarfism. CRF appears to be a small peptide and should be more applicable to commercial synthesis than the large HGH molecule. Patients with isolated growth hormone deficiency could have a deficiency or structural abnormality of either CRF or HGH. The recessive inheritance of this disease suggests that it is probably secondary to a structural mutation which produces an altered functionally inert peptide hormone. Purification and synthesis of CRF should provide a sensitive test to determine whether the primary defect lies in the hypothalamus or pituitary in these patients. In those forms of pituitary dwarfism associated with a primary hypothalamic lesion CRF administration may well turn out to be the treatment of choice. Purified or synthetic preparations of HGH, however, will still be required for the treatment of those forms of pituitary dwarfism associated with a primary pituitary defect or a structural abnormality in the HGH molecule.

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REFERENCES

1. McCann SM, Porter JC: Hypothalamic pituitary stimulating and inhibiting hormones. *Physiol Rev* 49:240-284, 1969
2. Schally AV, Redding TW, Bowers CY, et al: Isolation and properties of porcine thyrotropin-releasing hormone. *J Biol Chem* 244:4077, 1969
3. Abrams RL, Grumbach MM, Kaplan SL: The effect of administration of human growth hormone on the plasma growth hormone, cortisol, glucose and free fatty acid response to insulin: Evidence for growth hormone autoregulation in man. *J Clin Invest* 50:940-950, 1971
4. Peake GT, Rimoin DL, Packman S, et al: Feedback inhibition of growth hormone (GH) secretion in man. *Clin Res* 19:129, 1971
5. Kowarski A, Thompson RG, Migeon CJ, et al: Determination of integrated plasma concentrations and true secretion rates of human growth hormone. *J Clin Endocr* 32:356-360, 1971
6. Rabinowitz D, Merimee TJ, Burgess JA: Growth hormone-insulin interaction. *Diabetes* 15:905-910, 1966
7. Daughaday WH: Sulfation factor regulation of skeletal growth. *Am J Med* 50:277, 1971
8. Salmon WD Jr, Daughaday WH: A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage *in vitro*. *J Lab Clin Med* 49:825, 1957
9. Rimoin DL, Schimke RN: Genetic Disorders of the Endocrine Glands. St. Louis, Missouri, C. V. Mosby Co. In press
10. Hintz RL, Menking M, Sotos JT: Familial holoprosencephaly with endocrine dysgenesis. *J Pediatr* 72:81, 1968
11. Laron Z, Mannheimer S, Pertzalan A, et al: Serum growth hormone concentration in full term infants. *Israel J Med Sci* 2:770, 1966

12. Hoyt WF, Kaplan SL, Grumbach MM, et al: Septo-optic dysplasia and pituitary dwarfism. *Lancet* 1:893, 1970
13. Lahey ME, Kenny FM, Drash AL: Short stature and growth hormone deficiency due to histiocytosis—X. Abstracts of the Annual Meeting of the Society for Pediatric Research, 1970
14. Steiner MM, Boggs JD: Absence of pituitary gland, hypothyroidism, hypoadrenalism and hypogonadism in a 17-year-old dwarf. *J Clin Endocr* 25:1591, 1965
15. Stocks AE, Martin FIR: Pituitary function in haemochromatosis. *Am J Med* 45:839, 1968
16. Rimoin DL, Merimee TJ, Rabinowitz D, et al: Peripheral subresponsiveness to human growth hormone in the African pygmies. *New Eng J Med* 281:1383, 1969
17. Najjar SS, Khachadurian AK, Ilbawi MN, et al: Dwarfism with elevated levels of plasma growth hormone. *New Eng J Med* 284:809-812, 1971
18. Costom BH, Grumbach MM, Kaplan SL: Effect of thyrotropin-releasing factor (TRF) on serum TSH: An approach to distinguishing hypothalamic from pituitary forms of idiopathic hypopituitary dwarfism. Abstracts of the 41st Annual Meeting of the Society for Pediatric Research, p 12, April, 1971

United or Separate?

THE REAL ISSUE IN THE POLL of the membership which is to be begun September 1 is whether organized medicine in California will remain united or will separate, with many individuals and groups going different ways. There are those who will contend that this is not the case and that all that is at stake is one more expression of opinion in support of voluntarism as against compulsion, this time over the question of whether a physician exercises enough free choice when he joins or does not join his county medical association, knowing that in doing so he also joins the California Medical Association and the American Medical Association, or whether this free choice should now be extended to give him the further option of joining or not joining the CMA and AMA. The question to be posed to the membership—"Do you favor or oppose retaining the present system of unified membership in your county society, CMA and AMA?"—addresses itself to the real question.

These are times of revolutionary change. We have only to look around us to sense the enormity of what is occurring. Many, if not most, of what are generally thought of as the stabilizing elements of a social system are being seriously eroded, if they are not actually crumbling. This is apparent in the law and courts, in the educational system, in respect for the military and the police, and in the authority of the churches, to

cite a few pieces of the evidence. It is no longer possible to oppose or prevent this revolution. We are engulfed in it. Its hallmark so far has been fragmentation of the old order with little to propose for the new. The problems to be resolved are human problems and the needs to be met are human needs. Health and well-being are among the goals which are being sought. Medicine should take part in developing some of the new solutions. The question to be decided is how can medicine best play its role—united, or separate and fragmented?

Do not the issues of "voluntary" and "compulsory" seem somehow beside the point in the face of social revolution and cultural fragmentation? Everyone knows how physicians feel about free choice and compulsion. It has been voted on many times and in many ways. And it is a matter of record that both CMA and AMA have worked for voluntarism and against compulsion for as long as anyone can remember, and quite successfully too. Is this not a time to close ranks and not to scatter, to be united and not to separate? We should all favor retaining the present system of unified membership in county society, CMA and AMA.

Dealing in Futures

Part II—In Democratic Societies

A PREVIOUS EDITORIAL expressed the view that California and the country as a whole were investing in medical research and education as though only for today's market when actually they are dealing in futures—that is, spending money which has to be spent or invested today in order to buy or produce a product which can only be delivered at a later time when presumably it will be needed. The purpose of this editorial is to draw attention to a characteristic of democratic societies, be they institutions, organi-

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